ute to the optimization of its dosing. The aim of this study was to evaluate the influence of genetic and clinical factors on TAC pharmacokinetic variability in stable pediatric renal transplant patients.
Patients (or Materials) and Methods: This study was nested in a previous Prograf® to Advagraf® conversion clinical trial in pediatric patients (Eudra CT: 2009-017600-89). Tacrolimus pharmacokinetic analysis was performed using a noncompartmental analysis. *CYP3A5* (*3 rs776746 C>G), *ABCB1* (rs1045642 C>T), *POR* (*28 rs1057868 C>T and rs2868177 A>G) genotypes were determinate by RT-PCR using commercial Taqman® assays. The impact of individual genetic variants on TAC AUC0–24 (adjusted by administered dose/kg) was evaluated and an additive unweighted genetic score was build. Multivariate linear regression was performed including genetic (genetic score), demographic, and clinical information as independent variables and TAC weight-adjusted apparent oral clearance as dependent variable.
Results: Twenty-one kidney transplant pediatric patients (aged between 4 and 17 years) on stable TAC dose were included (12 males and 9 females). Mean (SD) body weight was 42.85 (15.42) kg. Subjects homozygote for CYP3A5*3 and the carriers of rs1045642, rs1057868, or rs2868177 have higher exposure to TAC than noncarriers ($P < 0.05$). Genetic score groups was as follows: 0 (Group 1), 1 (Group 2), 2 (Group 3), 3 (Group 4), and 4 (Group 5) genetic variants in *CYP3A5, ABCB1*, and *POR* genes. There was an increase in TAC dose/kg adjusted AUC as the number of variants in genetic score increase (tendency $P = 0.023$) and its value is 288% higher in group 5 compared with group 1. Genetic score, BMI, and concomitant deflazacort use were the only covariates retained in the multivariate regression model that explained 64.4% of weight-adjusted apparent oral clearance total variability. Genetic score, the concomitant deflazacort use and BMI explained 33%, 18%, and 15.4% of the total variability, respectively. Mean absolute error (SD) of the predicted weight-adjusted apparent oral clearance was of 32.82% (23.36%).
Conclusion: Genetic score composed by variants in *CYP3A5, ABCB1*, and *POR* genes, along BMI and concomitant deflazacort use, explain a clinically significant amount of the variability in oral clearance of tacrolimus. Larger studies are needed to evaluate the potential utility of these variables in predictive TAC dosing algorithms.
Disclosure of Interest: None declared.

PP133—PHARMACOGENETICS OF THE HUMAN SEROTONIN TRANSPORTER

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Introduction: The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) 5-HT is actively cleared from synaptic spaces by SLC6A4, a high-affinity, Na+-, and Cl--dependent transporter localized in presynaptic neuronal membranes. This brain 5-HT transporter appears to be a principal site of action of many antidepressant drugs including those of the tricyclic, SSRIs, and SSNRIs class. Many patients with depression are drug resistant. We hypothesized that changes in the transporter protein due to coding single nucleotide polymorphisms (SNPs) in *SLC6A4* may affect transporter–drug interactions and thus may contribute to the resistance to antidepressant drug treatment.
Patients (or Materials) and Methods: We screened SNP databases (dbSNP, 1000 Genomes, *ESP*) for natural variants in the human *SLC6A4* gene. We specifically focused on nonsynonymous SNPs (nsSNPs); that is, SNPs located in coding regions and resulting in amino acid variation in protein products of genes. The impact of amino acid substitutions caused by nsSNPs in *SLC6A4* on the structure and function of SERT was investigated by using 6 different in silico prediction tools. Based on the crystal structure of the bacterial homologue LeuT, a homology model of SERT was performed, and the positions of the amino acid substitutions relative to the proposed substrate binding pocket were identified. A rating scale integrating results from in silico predictions and 3D modeling was applied to extract those nsSNPs with a potentially high impact on the structure and function of SERT. For future in vitro testing in transfected cells, these mutations were inserted in an expression vector by site-directed mutagenesis.
Results: We identified 6 nsSNPs within the *SLC6A4* gene with potential effects on protein function. Two of them (H143Y and R144Q) reside nearby the cytoplasmatic pore between helix 2 (H2) and H3, which is involved in substrate binding. In both cases, the mutation results in a charge change and most likely in an altered pore opening of SERT. The third SNP (isoleucine 179 to valine) protrudes into the predicted binding cavity of inhibitor and substrate and therefore may influence substrate–transporter interaction. Another SNP causes the expression of a polar threonine 270 instead of a hydrophobic isoleucine also projecting into the cytoplasmic pore region. The P339L SNP is expected to destabilize H6, which is involved in substrate and inhibitor binding. The V488M SNP in H10 is close to the extracellular pore and may affect antidepressant binding.
Conclusion: By applying a comprehensive screening approach, we identified 6 naturally occurring nsSNPs that are expected to affect substrate (5-HT) and inhibitor (antidepressant drug) binding to SERT. We generated transiently transfected cell lines expressing the 6 variants. Future experiments will have to demonstrate the effects of these SNPs on SERT expression and transport function. Of particular interest is the impact of the variants on the inhibition of SERT by antidepressant drugs.
Disclosure of Interest: None declared.

PP134—ESOMEPRAZOLE USED AS A BOOSTER IN A HIV ULTRARAPID CYP2C19 METABOLIZER TREATED WITH VORICONAZOLE

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Introduction: Voriconazole, an antifungal agent, is metabolized by CYP450 2C19 (CYP2C19). CYP2C19 activity is modulated by drug–drug interactions (DDI) and genetic polymorphisms. We report a case of therapeutic use of esomeprazole that "boosted" voriconazole plasma concentrations in a CYP2C19 ultrarapid metabolizer HIV patient treated with a CYP2C19 inducer among her antiretroviral treatment (HAART).
Patients (or Materials) and Methods: A 35-year-old African female was diagnosed with AIDS in May 2012. A duodenal histoplasmosis and cryptococcosis infections were treated from June 2012 with a 3-week regimen of amphotericin B–flucytosine then oral voriconazole 100 mg BID. HAART was initiated (emtricitabine, tenofovir, and raltegravir). Voriconazole doses were increased and given intravenously (4 mg/kg/12 h IV) as she developed a single large intracranial mass. Several voriconazole trough concentrations (C_0) were measured below the therapeutic range (1.0–4.0 µg/mL). CYP2C19 genotype was tested and came heterozygous for the variant allele *CYP2C19*17*, which is associated with an ultrarapid phenotype. A treatment with esomeprazole 40 mg BID was started and titrated because of severe epigastralgia (histoplasmocytosis). Subsequent voriconazole C_0 were within the therapeutic range. After the proton pump inhibitor was switched to ranitidine, voriconazole C_0 were again infratherapeutic despite an increase in voriconazole doses.

Besides several changes in HAART were needed due to resistance or persisting replication. After the last change in HAART (darunavir-ritonavir),voriconazole C_0 decreased to 0.25 mg/L (50% decrease). Eventually, ranitidine was replaced by esomeprazole 40 mg IV BID. Three days later, voriconazole C_0 increased 14-fold and voriconazole dose could be reduced by 50% to 100 mg (2.5 mg/kg) BID. There were no other medication changes. Subsequent voriconazole C_0 stayed within the therapeutic range.

Results: Voriconazole systemic exposure depends on various factors among which CYP 450 activity influenced by genetic polymorphisms and DDI. Our patient was heterozygous for the *CYP2C19*17* variant allele, which has been associated with lower voriconazole AUC compared with wild-type individuals. However, her phenotype indicated a reduced activity of CYP2C19.

The change in voriconazole concentrations cannot be explained by a DDI with another drug of the antiretroviral treatment.

Conclusion: We report the case of an HIV patient with disseminated fungal disease who achieved targeted voriconazole C_0 using esomeprazole as a "booster" to overcome an ultrarapid CYP2C19*17/*1 genotype and a treatment by a CYP2C19 inducer such as ritonavir. Further evaluation is warranted for this "boosting strategy" to define the right booster dose, the relevance of this effect in rapid metabolizers and eventually transferability in clinical setting.

Disclosure of Interest: None declared.

PP135—PHARMACOMETABOLOMICS FOR INDIVIDUALIZED TREATMENT OF ALCOHOLISM: HIGH SERUM GLUTAMATE LEVEL IS ASSOCIATED WITH POSITIVE RESPONSE TO ACAMPROSATE TREATMENT

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Introduction: Acamprosate, a homo-taurine analogue, is approved for treatment of alcohol dependence. Meta-analyses favor acamprosate for its ability to support abstinence, which is the most stable type of remission in alcoholics. Yet, only a limited number of treatment-seeking alcoholics use acamprosate, most likely because of individual differences in response and the lack of response predictors.

Patients (or Materials) and Methods: We used a pharmacometabolomics approach to investigate metabolic response in serum amino acid metabolites (including acamprosate) between responders and nonresponders to acamprosate treatment. Serum samples were collected before and after 3 months of acamprosate treatment. Efficacy was defined by self-reported abstinence during acamprosate treatment and average γ-glutamyl transferase (GGT) levels at baseline and 3-month follow-up were used to confirm abstinence. Of those, 14 responders and 18 nonresponders comprised an investigation cohort and an additional 30 responders and 28 nonresponders comprised a replication sample.

Results: Initial metabolite screening was conducted using 32 alcohol-dependent subjects. Glutamate levels were significantly higher at baseline in the 14 responders compared with the 18 nonresponders [$t(30) = 2.7$, $P < 0.05$]. After acamprosate treatment, serum glutamate levels in the responder group significantly decreased compared with baseline [$t(26) = 3.3$, $P < 0.05$). Similarly, in a replication sample of 58 additional alcohol-dependent subjects, responders had significantly higher glutamate levels at baseline compared with the nonresponder group [$t(88) = 2.8$, $P < 0.05$], which decreased significantly after acamprosate treatment [$t(86) = 3.6$, $P < 0.05$].

Conclusion: Our findings suggest that high glutamate levels may be a biomarker to predict the efficacy of acamprosate treatment in alcohol-dependent subjects.

Disclosure of Interest: None declared.

PP136—GENETIC POLYMORPHISM OF CYP2D6 SIGNIFICANTLY AFFECTS THE PHARMACOKINETICS OF TOLPERISONE

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Introduction: Tolperisone, a centrally acting muscle relaxant, is used for relieving spasticity of neurological origin and muscle spasm associated with painful locomotor diseases. Tolperisone is mainly metaolized by CYP2D6 and CYP2C19, CYP1A2, and CYP2B6 are also involved in the metabolism of tolperisone. CY2D6 is responsible for variablility of drug response, largely due to genetic polymorphism. Therefore, we investigated the effects of *CYP2D6* genetic polymorphism on the pharmacokinetics of tolperisone.

Patients (or Materials) and Methods: Thirty healthy Korean subjects were selected and they were divided into 3 different groups according to *CYP2D6* genotype, *CYP2D6*wt/*wt (*wt= *1* or **2*, n = 10), *CYP2D6*wt/*10* (n = 10) and *CYP2D6*10/*10* (n = 10). After overnight fasting, each subject received a single 150-mg oral dose of tolperisone. Blood samples were collected up to 12 hours after drug intake, and plasma concentrations of tolperisone were determined by using LC-MS/MS analytical system.

Results: C_{max} and AUC_{inf} of tolperisone in *CYP2D6*10/*10* genotype group was significantly higher than those in *CYP2D6*wt/*wt* group ($P = 0.0007$ and $P = 0.0002$, respectively). Apparent oral clearance (CL/F) of tolperisone in *CYP2D6*wt/*10* and *CYP2D6*10/*10* group was 64% and 75% lower than that in *CYP2D6*wt/*wt* group ($P < 0.001$ and $P = 0.0001$, respectively). Among 3 genotypes, differences in $t_{1/2}$ of tolperisone were not statistically significant.

Conclusion: Tolperisone is mainly metabolized by *CYP2D6* and *CYP2D6* genetic polymorphism has a significant impact on the pharmacokinetics of tolperisone.

Disclosure of Interest: None declared.

PP137—EFFECTS OF THE GENETIC POLYMORPHISMS OF HUMAN MULTIDRUG AND TOXIN EXTRUSION 1 (HMATE1/SLC47A1) TRANSPORTER ON THE RENAL TUBULAR SECRETION OF N1-METHYLNICOTINAMIDE

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Introduction: Human multidrug and toxin extrusion 1 (hMATE1/*SLC47A1*) transporter may be involved in the active elimination clearance of many cationic drugs in the kidneys. Scarcity of knowledge about endogenous substrates of hMATE1 appears to hinder exploration of the roles of genetic polymorphisms on the functional activity of hMATE1.

Patients (or Materials) and Methods: Fifty-four healthy volunteers (32 males and 22 females; 23 [2] years) underwent 3-hour timed-urine collection and blood drawing at the midpoint. Plasma and urinary levels of N_1-methylnicotinamide (MNA) and creatinine were measured with a liquid chromatography-mass spectrometry system. Renal tubular secretion clearance of MNA ($C_{LTS,MNA}$) was calculated by subtracting the renal clearance of creatinine (a substitution of glomerular filtration rate) from that of MNA. Genetic variants of hMATE1/*SLC47A1* and another renal cation transporter, hOCT2/*SLC22A2*, were genotyped by polymerase chain reaction followed by direct sequencing. The protocol of the present study was